REMARKS

Claims 1-18 are pending herein and stand rejected under 35 U.S.C. §§ 112 and 103. In view of the arguments below, Applicants believe the amended claims are in condition for allowance. Reconsideration is respectfully requested.

Amendments to the Claims

Solely to expedite prosecution of the application, Applicants have amended the claims as set forth above. Claims 1, 7 and 13 have been amended for clarity. The amendments to the claims are fully supported by Applicant's originally filed specification and claim set; see for example page 2, line 21 through page 3 line 4. No new matter has been added to the application as a result of the above claim amendments.

The Rejection under 35 U.S.C. § 112, first paragraph—Enablement Requirement

The Examiner has rejected claims 1-18 under 35 U.S.C. § 112, first paragraph, for lack of enablement. While the Examiner admits that the specification is enabling for use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, the Examiner argues that the specification does not provide enablement for targeting a nucleic acid to a site in a patient, inhibition of TGFβ2 *in vivo* or treatment of a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2. Applicants have amended Claims 1, 7 and 13 to further clarify the claimed invention.

The first paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), as long as the amount of experimentation required is not "undue experimentation". *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir.1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The Examiner agrees that the specification does provide guidance regarding the pharmacokinetics of representative nucleic acid ligands in rats, teachings of the isolation of nucleic acid ligands that bind human TGFβ2, teachings of therapeutic compositions and guidance on post-SELEX modifications that improve *in vivo* stability. However, the Examiner cites Opalinska et al., stating that this reference illustrates the issues of delivery recognized in the art. Applicants assert that the delivery of nucleic acid ligands *in vivo* is not addressed in Opalinska et al., and that this reference does not describe the state of the art with regard to nucleic acid ligands.

In the abstract, Opalinska et al., specifically states, "This article reviews different strategies for ***modulating gene expression***, and discusses the successes and problems that are associated with ***this type*** of therapy." Opalinska at 503. Further, the article states,

> Nucleic-acid-mediated gene silencing has been used with great success in the laboratory, and this strategy has also generated some encouraging results in the clinic. Nevertheless, it is widely appreciated that the ability of nucleic-acid molecules to ***modify gene expression*** in vivo is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells, and identification of sequence that is accessible to hybridization in the genomic DNA or RNA. Intuitively, DNA accessibility is limited by compaction of nuclear material and transcription activity of the gene target.

Opalinska at 511. (emphasis added)

Thus Opalinska is limited to discussing the efficacy of nucleic acid gene therapy. Nucleic acid ligands are not designed to work *in vivo* in a similar manner to that of nucleic acids for gene targeting. The issues associated with the therapies are completely different. Nucleic acid ligands are not naturally occurring substances and they are not designed to alter gene expression. Instead they are non-naturally occurring molecules that are designed to modulate the activity of proteins. In the present case, TGFβ2 is the target for the nucleic acid ligand-- an *extracellular* target. The amendments to Claims 1, 7 and 13 further clarify that TGFβ2 is an extracellular target. The nucleic acid ligand is not delivered into any cells. Thus, reference to cellular delivery is totally irrelevant.

The Office Action states, "While it may be correct that nucleic acid ligands do not have a mechanism of action identical to that of antisense nucleic acids, nucleic acid ligands are

nevertheless nucleic acids; difficulties encountered in delivery of nucleic acids to cells would be the same for nucleic acid ligands as for antisense oligonucleotides." (Office Action at 3). Applicants respectfully disagree. To begin, the Office Action has understated the difference between the mechanisms of action of nucleic acid ligands versus antisense nucleic acids. It is not just that the mechanisms of action are *not identical*; the mechanisms of action are *completely different*. Due to the extreme difference in mechanism of action, difficulties encountered in the delivery of antisense nucleic acids into cells, and further into the nucleus of cells to accomplish nucleic-acid-mediated gene silencing are not relevant to the delivery of nucleic acid ligands to the extracellular target of TGFβ2. Primary structure of the antisense oligonucleotide is of utmost importance for nucleic acid-mediated gene silencing. In all of the examples given in Opalinska, the primary sequence of the nucleic acid is necessary for targeted inhibition. Maintaining accessibility of that primary sequence for delivery to the target *in vivo* was shown to be problematic. With regard to delivery of nucleic acid ligands, the tertiary structure of the nucleic acid ligand is determinate of target binding –considerations regarding accessibility to primary sequence are not an issue. Thus, the difficulties encountered in delivering antisense oligonucleotides into cells *in vivo* are not relevant to delivery of nucleic acid ligands to an extracellular target *in vivo*.

The specification provides guidance regarding the pharmacokinetics of representative nucleic acid ligands in rats, teachings of the isolation of nucleic acid ligands that bind human TGFβ2, teachings of therapeutic compositions and guidance on post-SELEX modifications that improve *in vivo* stability. Thus, the specification is enabling. Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 103, Obviousness

The Examiner has rejected Claims 1 and 3-5 as being unpatentable over Gold et al., (US 5,270,163) in view of Tullis (WO 88/09810) and Shah et al. (Journal of Cell Science 1995). The Examiner bears the burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. In determining obviousness, one must focus on Applicant's invention as a whole. Symbol Technologies Inc. v. Opticon Inc., 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). According to the MPEP § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations." Obviousness cannot be established by combining teachings in the prior art, absent some teaching or suggestion in the prior art that the combination be made (*In re Stencel* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell* 891 F. 2d 899, 13 USPQ2d 1248 (Fed. Cir.1989)).

Gold et al. teach a method of identifying nucleic acid ligands, Tullis teaches nucleic acid (*not* nucleic acid ligand) conjugates comprising an antisense conjugated to a solubility-modifying moiety, and Shah et al. teach that TGFβ2 is one TGFβ isoform that has a role in cutaneous scarring.

Inhibiting TGFβ2 comprising contacting said TGFβ2 with a nucleic acid ligand of TGFβ2 is not a predictable result in view of Gold et al., Tullis and Shah et al. The fact that an antibody interferes with TGFβ2 action, and in this case may affect scar tissue formation, does not predict success for an entirely different moiety, i.e., a nucleic acid ligand, which binds through a different mechanism. Accordingly, success for the instant invention cannot be predicted.

Further, the addition of PEG, as denoted in Claims 3 and 5, is not obvious in view of Tullis and Gold. The Tullis reference teaches novel nucleic acid conjugates for "inhibiting

intracellular mRNA maturation . . .[c]onjugates comprise a relatively short oligonucleotide sequence, a linking group, and a group which modifies the HLB (hydrophilic lipophilic balance) to provide an amphiphilic product." *See* WO 88/09810, page 4, lines 1-8 (emphasis added). Tullis teaches the use of nucleic acid conjugates in relation to **intracellular** events. Further, Tullis discloses, "the amphiphilic nature of the product [nucleic acid conjugate] aids in the transport of the conjugate across the cellular membrane, and can provide additional advantages, such as increasing aqueous or liquid solubility of nucleic acid derivatives, e.g., use of an amphiphilic group to enhance water solubility of long chain methyl phosponates and stabilizing *normal* nucleic acids to exonuclease digestion." *Id.*, at lines 9-15 (emphasis added). Thus, Tullis is limited to conjugates having an increased ability to be transported across the cellular membrane, and to increase the water solubility and *normal* nucleic acid stability of the conjugate to exonuclease digestion.

The teachings of Tullis to utilize conjugates for enhanced membrane transport or stability of *normal* nucleic acids with regard to exonuclease digestion is not applicable. The present invention teaches the use of conjugates for modifications yielding a higher stability in serum and animals. As discussed above, nucleic acid ligands targeting a growth factor have an entirely different mode of action than nucleic acids targeting genomic DNA. The present invention is directed towards molecules having a non-intracellular target; TGFβ2. TGFβ2 is an extracellular moiety; the ability to cross the cellular membrane (as in the case of nucleic acids targeting genomic DNA) is not an issue. Nucleic acid ligands are not normal nucleic acids. As such, there is no motivation to combine the properties of Tullis (to increase cellular uptake of nucleic acids) where the nucleic acid ligand target is secreted. In fact, doing so (i.e., increasing the cellular uptake) would be entirely counter to the entire purpose of this invention.

The Examiner has stated that, "...the reasonable expectation of success in producing a nucleic acid ligand to TGFβ2 is provided by Gold et al. who teach their method of producing nucleic acid ligands is applicable to almost any target. The reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand is provided by Tullis, who teaches that such oligonucleotide conjugates can be made using routine synthesis methods." (Office Action at 7). However, there is an absence of predictable results with regard to

a TGFβ2 nucleic acid ligand that binds to and inhibits the function of TGFβ2 protein. Gold et al. teaches the SELEX method which identifies nucleic acid ligands solely on the basis of their ability to bind a target. Although Gold et al. teaches the SELEX method, the teachings of Gold et al. cannot predict a functional nucleic acid ligand to TGFβ2. Thus, the disclosure of Gold et al. does not contain a sufficient teaching that the claimed result would be obtained if certain directions were pursued. There was nothing in the art to suggest the functionality of the TGFβ2 nucleic acid ligand.

Tullis teaches antisense oligonucleotide conjugates. Nucleic acid ligands are not equivalent to the nucleic acids described by Tullis. Nucleic acid ligands are an art-recognized class of molecule characterized by being nucleic acids that exhibit high specificity binding (typically in the nM or pM range) to a given target molecule. As discussed previously, although nucleic acid ligands are nucleic acids they represent an entirely different class of molecule to those nucleic acids that are important for the storage of information, or those that bind other nucleic acids purely upon complementary base pairing. Antisense nucleic acids do not rely on their three-dimensional shape to bind their complementary sequences. In the case of nucleic acid ligands, the three dimensional structure of the nucleic acid ligand is of key importance. A nucleic acid ligand will only bind target when it has assumed a complex three-dimensional structure, much like a denatured antibody cannot bind its target. Applicants submit that there was no reasonable expectation of success for a complex comprising a TGFβ2 nucleic acid ligand and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound. The obvious problem of disruption of three dimensional structure of the nucleic acid ligand with the addition of a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound precludes any reasonable prediction of a successful result.

Thus, a reasonable expectation of success was not found in the prior art. Neither Tullis nor Gold provides predictability with regard to inhibition of TGFβ2. Gold does not provide predictability with respect to a functionally active (i.e., inhibitory) nucleic acid ligand. Tullis does not provide predictability that a nucleic acid ligand to TGFβ2 will maintain its tertiary structure; Tullis does not provide a finite number of identified, predictable solutions with a reasonable expectation of success to create a TGFβ2 nucleic acid ligand that will maintain its

tertiary structure with a conjugate and inhibit TGFβ2. As such, the present claimed invention is not obvious in view of Gold et al., Tullis and Shah et al. Reconsideration is respectfully requested.

Closing Remarks

Applicant believes that the pending claims, as amended above, are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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